# 3 Pain in Preverbal Children

Erroneous assumptions have hampered efforts to assess and manage pain effectively in chil-dren. A prevalent belief is that children do not ex-perience pain on the assumption that incomplete mye-linization of nerve fibers precludes the transmission of pain impulses. Prevalent myths reveal the potency of this assumption: (a) young children are unable to sense pain neurologically; (b) they do not interpret noxious stimulation as pain; and (c) they do not ex-perience the deleterious consequences of severe pain in the same way that adults do (Schechter, 1984).

Results of neuroscience research on animal models and clinical research on preterm and term neonates challenge these myths. Neuroscience re-search has documented the intactness and functional ability of the neuroanatomical apparatus and the neurochemical systems used for pain transmission and modulation in children (Anand, 1990; Anand, Phil, & Carr, 1989; Fields, 1987; Fitzgerald, 1987, 1991a, 1991b). Clinical research has shown that preterm neonates can mount stress responses to noxious stim-uli (Anand, Brown, Bloom, & Aynsley-Green, 1985; Anand, Brown, Causon, Christofides, Bloom, & Aynsley-Green, 1985) and that these stress responses can be blocked with analgesics (Anand, Sippell, & Aynsley-Green, 1987). The argument that preverbal children do experience pain relies on research that demonstrates the presence of intact neural pathways for pain transmission and modulation and the occur-rence of physiological and behavioral responses to invasive stimuli such as surgery, injections, and heel lances.

Cutaneous pain, in which the noxious stimulus is evident, and the related physiological and behavioral responses can be identified, is the focus of most research on preverbal children. That their phy-siological and behavioral responses are indicators of stress but more specifically pain can be postulated. The argument for the stress response being pain is supported by research demonstrating that the physio-logical and behavioral responses can be obliterated or attentuated in the presence of analgesia and anesthe-tic.

Cutaneous pain for this discussion relies on the work of Fitzgerald (1991a, 1991b), which expanded Field's (1987) perspective on cutaneous pain response as the first pain and second pain to include three types of pain: immediate, established, and long term. Surgery, injury, or an invasive procedure evokes an *immediate* pain response that lasts milli-seconds or minutes. The *established* pain response accompanies the inflammatory process that occurs af-ter the immediate response, i.e., the pain after an invasive procedure, surgery, or injury. This pain may last for a few hours to several days. The *long term* response is residual pain that continues beyond the inflammatory process; little is known about this pain response. Theoretically it may involve perma-nent structural changes in the neurological system and occur over weeks, months, or possibly throughout the lifespan (Fitzgerald, 1991b).

Little research has focused on other types of pain (visceral, deep somatic, and neuropathic). The noxious stimuli in these types are not obvious and preverbal children are unable to provide verbal descriptors that might help to distinguish among them.

Research findings should be interpreted within the contextual nature of the pain because phy-siological and behavioral manifestations may differ according to type of pain. Differences in these mani-festations may affect clinical approaches to assess-ment and management.

## State of the Science

### *Dimensions of the Pain Experience*

For preverbal children, comprising preterm and term neonates, infants, and toddlers, emphasis is on the physiological and behavioral dimensions of the pain experience. The sociocultural dimension, how-ever, also is important because parents and other family members are often involved in caring and decision-making for preverbal children. Little re-search is available on this dimension.

### *Physiological Dimension*

***The Neural System.*** While the neonate's neural system for pain transmission and modulation is intact and functional, research has revealed some pertinent developmental issues. Myelination of nerve fibers is incomplete in preterm and term neonates and perhaps young infants (Anand et al., 1989). The primary afferent axons in the peripheral nerves vary in size and degree of myelination and include large myelinated fibers (Aá), small myelinated fibers (Aä), and small unmyelinated fibers (C). The A fibers, however, are not myelinated at birth; myelination occurs during the early months of infancy (Anand et al., 1989; Fitzgerald, 1987). Incomplete myeliniza-tion, however, does not alter pain perception because the lack of myelination "merely implies a slower con-duction velocity in neonatal nerves or central nerve tracts, which is offset completely by the shorter inter-neuron and neuro-muscular distances traveled by the impulse" (Anand, 1990, p. 114). Hence, despite the incomplete myelination, young infants appear to have the appropriate peripheral and central neural mech-anisms to encode pain.

***Nociception and the Neural System.*** Nociceptors are present at 24 weeks of human gestation (Fitzgerald, 1991a). The polymodal receptors at 40 weeks are comparable to adult firing frequencies and response patterns. The mechano-receptors (which respond to firm pressure on the skin) exhibit limited firing frequency in the neonatal period. Fitzgerald (1987) postulated that the low firing may occur secondary to the incomplete myelination.

The C fibers are mature from an anatomical and neurochemical perspective but their full physiological function occurs slowly during the postnatal period (Fitzgerald, 1991a). Of particular concern is insensitivity to chemical skin irritants and the limited ability to produce neurogenic edema (Fitzgerald & Gibson, 1984). This finding implies that sensitivity to pain increases as the physiological function of the C fibers reaches maturity. The neonatal period is critical for this maturation to occur.

In the rat model, receptive fields in the neonatal dorsal horn are larger than in older rats (Fitzgerald, 1985). This physiological finding may account for the low pain threshold and the weak im-mediate response to nociception in human neonates (Fitzgerald, 1991a). Fitzgerald demonstrated that the pain threshold was low in premature infants. For example, the flexor reflex in the preterm "can be activated by low inputs" and as such is "not an exclu-sive measure of nociception function" (Fitzgerald, Shaw, & MacIntosh, 1988, p. 524). In fact, the flexor can be triggered by repeated handling that evokes "excessive excitation of central neu-rons...which could contribute to uncontrolled changes in blood pressure" (Fitzgerald et al., 1988, p. 524).

Fitzgerald, Millard, and MacIntosh (1989) showed that human neonates subjected to repeated heel lances on one foot exhibited a pain threshold lower in the injured foot than in the noninjured foot. Treatment of the affected foot with a local anesthetic cream raised the pain threshold. Other research by Fitzgerald (1991a, 1991b) demonstrated that the re-sponses of human neonates to nociception are likely to be unpredictable, imprecise (or nonspecific), and disorganized. As such, immediate pain responses ex-hibited by neonates may be misinterpreted. In fact, noxious stimuli may "alter the sensitivity of the infant to other somatic inputs and render him or her hyper-algesic" (Fitzgerald, 1991a, p. 259).

Endogenous pain control mechanisms in the descending pain-modulating circuits that dampen pain impulses appear to be lacking or immature in the young infant. Serotonin (5HT) is a biogenic amine transmitter that serves an important role in pain modulation. It produces analgesia by modulating ascending nociceptor systems in the dorsal horn (Fields, 1987). Serotonin levels in the young infant are low and may limit the effectiveness of the endo-genous pain control mechanisms (Fitzgerald, 1991b). These findings led Fitzgerald (1991b) to speculate that the established pain in the neonate could be worse than the observed pain response.

The plasticity of the nervous system in the young infant may not be a positive attribute. According to Fitzgerald (1991b), painful stimuli can cause permanent structural changes. Small peripheral nerve damage may occur with procedures such as chest tube insertion. During invasive procedures, sensory neurons may die and cause holes in what Fitzgerald calls the body map. To compensate for a hole in the body map, a structural reorganization of the surrounding neurons occurs, resulting in a gross overrepresen-tation of body area when pain occurs in that area. The reorganized neurons fail to thrive in size and form. Such structural changes may affect the child's long term development. These findings and specula-tions, however, need clarification and verification through further research.

Neuroscience research primarily using animal models suggests that the neural pathways for pain in preterm and term neonates are neuro-anatomically intact (Anand, 1990; Anand et al., 1989; Fitzgerald, 1991a, 1991b). Of importance, however, are the findings that preterm and term neonates: (a) exhibit unpredictable, imprecise, disorganized, and weak behavioral responses to pain secondary to the continuing postnatal development of the neurological system; (b) may lack the ability to modulate effectively pain through endogenous mech-anisms; and (c) may experience long-term structural changes in the neurological system secondary to un-treated pain. With maturing neural pathways, older infants and toddlers: (a) exhibit more precise, more organized, and stronger behavioral responses to pain; and (b) may have the ability to modulate pain more effectively.

***The Stress Response***. Clinical research has shown the ability of preterm neonates to mount stress responses to noxious stimuli (Anand, 1990; Anand, Brown, Causon, Christofides, Bloom, & Aynsley-Green, 1985). In two studies, Anand and colleagues (Anand, Brown, Bloom, & Aynsley-Green, 1985; Anand, Brown, Causon, Christofides, Bloom, & Aynsley-Green, 1985) showed cardiovascular, endocrine, and metabolic responses to surgery in preterm and term neonates. Term neonates responded to superficial, intra-abdominal, and intra-thoracic surgery with increased plasma levels of adrenaline and noradrenaline. In adults, noradrenaline also increases but adrenaline falls or remains stable following surgery. Thus the increase in adrenaline in neonates is of concern. Both term and preterm neonates developed hyperglycemia but preterm neonates also developed hyperlactemia. Anand and colleagues postulated that the hyper-lactemia corresponded to a deficiency in hepatic enzymes in preterm infants. They proposed that an increase in adrenaline during surgery triggers the hyperglycemic response, and the glucagon secretion during the postoperative period maintains it. Con-comitantly, the lack of insulin secretion during surgery and the early postoperative period creates an imbalance between the circulating glucose and insulin. For term neonates, insulin levels increased at 12 and 24 hours postoperatively, restoring the glucose-insulin balance to normal levels. A hyperglycemic response can cause an increase in plasma osmolality resulting in deleterious effects on the renal cortex and cerebral substance, possibly leading to intraven-tricular hemorrhage. Insulin levels did not return to normal in the preterm neonates, thus placing them at greater risk for subsequent problems from hyper-glycemia and hyperlactemia. Subsequent research showed that analgesia during the operative period blocked these potentially deleterious responses (Anand, Sippell, & Aynsley-Green, 1987). This body of research provides a compelling argument that preterm and term neonates can mount a stress re-sponse to nociception (e.g., through surgery) and that long- and short-term effects of untreated and unre-solved pain may be harmful, especially in preterm neonates. Analgesia, however, can block or diminish the stress response and the harmful sequella.

### *Behavioral Dimension*

Behavioral competency within preterm and term neonates, infants, and toddlers varies considerably; therefore, behavioral responses to pain may differ. While crying is a common way for preverbal children to communicate distress, other vocalizations such as whining evolve during the first year of life. By the end of toddlerhood, verbal communication may include the use of terms such as "boo-boo," "owie," and "hurt" and the child may be able to localize pain by pointing. Motor responses range from the flexion reflex in the preterm neonate to protection and resistance in the toddler. Behavioral competency must be considered in the development of approaches to measuring pain.

### *Framework for Reviewing Pain Research*

Important factors in addressing pain in the preverbal child are (a) the type of pain, (b) the developmental stage of the neural pathways for trans-mitting and modulating pain impulses, and (c) the behavioral competency of the child. To emphasize the importance of these factors, the critical analysis of the pain research literature is organized by type of pain: *Cutaneous Pain* and *Other Pain*. Within *Cuta-neous Pain*, two categories focus on the duration of the pain response: *Immediate* and *Established*. *Long Term Pain* is not discussed because the review of lit-erature did not yield any studies on this pain re-sponse. Only a few studies address visceral, deep somatic, and neuropathic pain; thus these studies are combined under one heading: *Other Pain*.

Further delineation occurs within each of these types and duration of pain according to develop-mental stage of the neural pathways and behavioral competency. Gestational and chronological age is assumed to approximate neural development and be-havioral competency allowing grouping according to the following groups: *Preterm Neonates*, *Term Neo-nates*, *Infants*, and *Toddlers*. The developmental stage of the neural pathways and behavioral compe-tency is important in characterizing the child's response to pain and potentially in understanding the efficacy of pain interventions.

### *Assessment and Management: Cutaneous Pain*

The majority of the research on pain and preverbal children focuses on cutaneous pain. Emphasis is on responses to nociception, approaches to measurement, and management with pharmacological and nonpharmacological strategies.

### *Preterm Neonates*

The <u>*immediate pain response*</u> in preterm neonates occurs with noxious stimulation of short duration. Studies on preterm neonates and nursing care procedures show that they respond to pain but that their responses may be misleading. In a case study analysis of 5,198 computerized caregiver-infant interactions (interrater reliability .85), Gorski, Hole, Leonard, and Martin (1983) reported on physiological and behavioral distress exhibited by a preterm infant under two conditions: chest physio-therapy and close social interaction. The preterm infant responded similarly under both conditions. The investigators postulated that the infant became too physically depleted to organize a behavioral response to the chest physiotherapy.

Beaver (1987) found that the simultaneous action of lancing the heel and stroking the medial side of the leg of eight preterm neonates was more aversive, according to heart rate, blood pressure, and transcutaneous oxygen ($TcPO_2$) than touching the heel with the blunt end of a lancet or lancing the heel. Heel lance elicited a drop in $TcPO_2$ in two studies (Beaver, 1987; Norris, Campbell, & Brenkert, 1982). However, Norris and colleagues (1982) found that changes in $TcPO_2$ did not differ significantly across time for the heel lance but did for suctioning and positioning, demonstrating that the type of procedure is important in alterations in $TcPO_2$.

Davis and Calhoon (1989) showed differences in the behavioral response of 12 premature infants to painful care and routine care. Painful care included a variety of stimuli including chest physiotherapy, insertion and removal of intra-venous lines, suctioning, bloodwork, change of car-diac leads, and dressing changes. Results showed that painful procedures elicited significantly more physiological arousal, negative facial expressions (i.e., a cry face or frown with or without crying), and large body movements than did routine care.

Preterm neonates in intensive care respond differently to invasive procedures according to their degree of illness. Field and Goldson (1984) ex-amined the use of a pacifier during heel lances with preterm neonates in minimal care ($n$ = 48) and pre-term neonates in intensive care ($n$ = 48). Pacified preterm infants in both settings were more quiet than unpacified preterm infants. The pacifier, however, did not favorably alter the physiological arousal (i.e., heart and respiration rates) of preterm infants in intensive care. This finding suggests that degree of illness may affect the behavioral response of preterm infants to intervention strategies but not the physio-logical response. In a study on neonates that inclu-ded six preterm infants, Rich, Marshall, and Volpe (1974) found minimal behavioral response to a series of pin pricks. Unlike term neonates, most preterm neonates moved only the stimulated leg (i.e., flexor reflex) and none cried or grimaced in response. These findings suggest that premature neonates exhibit an absence or diminution of generalized behavioral responses to painful stimuli. Crying may also be absent or diminished: spectrographic cry analysis revealed that the pain cry in preterms has a longer latency to onset (Zeskind & Lester, 1981) and is shorter in duration (Thodén, Järvenpää, & Michelsson, 1985; Zeskind & Lester, 1981).

Some studies suggest that premature neonates physiologically respond similarly across different stimuli while others suggest that they respond dif-ferently. Degree of illness appears to affect the physiological arousal. Behavioral responses of pre-term neonates to various stimuli are inconsistent. These incompatible findings are congruent with the theoretical perspective that neonates have large, nonspecific receptive neurological fields with imprecise and undifferentiated responses. In addi-tion, a characteristic response pattern does not appear to exist especially in regard to behavior.

The few studies with relatively small numbers preclude definitive conclusions on the immediate pain response by preterm infants and to potential intervention strategies such as stroking, close social interaction, and nonnutritive sucking. However, these studies suggest that preterm neonates (unless they are ill) may respond to noxious stimuli behaviorally and physiologically, but diminished and undifferentiated responses may occur.

This finding raises questions about the appropriate approach for measuring pain in preterm infants. More research on the development of reli-able, valid, and sensitive measures of pain is neces-sary. The development of the measures needs to con-sider the possibility that overstimulation (whether noxious or not) elicits aversive physiological respon-ses. Thus, approaches to pain measures may be limi-ted to nondisruptive, observational techniques. Potentially the pain measure needs to focus on subtle aspects of the behavioral and physiological responses of the preterm infant.

Management of pain in preterm infants is not well studied. Strategies that prevent the immediate pain response such as nonnutritive sucking and the use of pharmacologic agents are needed to minimize adverse metabolic, behavioral, and motor responses associated with unrelieved pain. For example, Friesen, Honda, and Thieme (1987) demonstrated that pancuronium and a general anesthetic (isoflurane, halothane, fentanyl, or ketamine) prevented increases in the anterior fontanel pressure during tracheal intubation. Untreated preterm infants exhibited in-creased pressure, thereby potentially subjecting them to the risk of intraventricular hemorrhage. Few studies, however, focus on the use of pharmacologic agents before and during such invasive procedures. Strategies to alleviate pain must be approached from a perspective that addresses pain relief while mini-mizing adverse effects.

The *established pain response* in preterm neonates is understudied. No assessment tools have been developed to measure pain in these neonates.

Anand and colleagues (Anand, Brown, Bloom, & Aynsley-Green, 1985; Anand, Brown, Causon, Christofides, Bloom, & Aynsley-Green, 1985) in studies involving small numbers of neonates showed that anesthetized preterm neonates were at risk for problems from hyperglycemia and hyper-lactemia up to 24 hours postoperatively. (See discussion under Stress Response). This finding led Anand, Sippell, and Ansley-Green (1987) to investi-gate whether the use of fentanyl anesthesia would alter the surgical stress response of preterm neonates (*n* =16). In a randomized controlled trial, the fentanyl group (*n* = 8) exhibited a dampened stress response. Plasma adrenaline fell during surgery and remained below preoperative levels for 24 hours postoperatively. Plasma noradrenaline levels rose during surgery but dropped postoperatively below preoperative levels. The plasma noradrenaline levels, although similar at the preoperative baseline, were always lower than those in the nonfentanyl group. During surgery, the insulin-glucagon molar ratio increased in the fentanyl group and decreased in the nonfentanyl group. Thus, the hyperglycemic re-sponse was significantly less in the preterm neonates receiving fentanyl, as was the blood lactate level. Clinically the preterm neonates in the fentanyl group exhibited fewer complications postoperatively. In the nonfentanyl group, more preterm neonates needed ventilatory support, experienced more hemodynamic or metabolic complications, and developed intra-ventricular hemorrhages. Collins, Koren, Crean, Klein, Roy, and MacLeod (1985) and Robinson and Gregory (1981) found fentanyl could be used safely and satisfactorily for preterms undergoing ligation of patent ductus arteriosus.

The assessment and management of the established pain response in preterm neonates has received minimal attention. Needs include: (a) more complete characterization of the premature infant's response to aversive and potentially painful stimuli; (b) development of reliable, valid, and sensitive clinical tools to measure pain; (c) determination of the safety, efficacy, and long-term effects of pharmacologic agents; and (d) study of the effective-ness of nonpharmacologic strategies. The need for more research is urgent because technology is advan-cing and younger preterm neonates are being saved, since premature neonates endure multiple invasive procedures resulting in established pain, and since surgery is inevitable for selected preterm neonates.

***Term Neonates***

The *immediate pain response* in term neonates includes crying, facial grimace, and body movement. While neonates respond to aversive stimuli, findings may differ according to type of aversive stimuli and the measurement strategies used. Three types of stimuli were imposed on the neonates for research purposes (i.e., pinpricks, rubber band snaps, and skin pinch) and also three types of stimuli that commonly occur in the health care of neonates: heel lance, injections, and circumcisions.

Studies of cries in response to the different noxious stimuli focused on *presence/absence* (e.g., Owens & Todt, 1984; Rich et al., 1974), *latency to cry* (e.g., Fisichelli, Karelitz, Fisichelli, & Cooper, 1974; Franck, 1986; Grunau & Craig, 1987; Grunau, Johnston, & Craig, 1990; Zeskind & Lester, 1978), *percent of time crying* (e.g., Fisichelli et al., 1974; Holve, Bromberger, Groveman, Klauber, Dixon, & Snyder, 1983; Wiliamson & Williamson, 1983), *duration of cry* (e.g., Franck, 1986; Grunau & Craig, 1987; Grunau et al., 1990; Porter, Miller, & Marshall, 1986; Zeskind & Lester, 1978), *cry cycle* (e.g., Franck, 1986; Fisichelli et al., 1974; Grunau & Craig, 1987), *cry motions* (Bosma, Truby, & Lind, 1965), and *acoustic parameters*, e.g., fundamental frequency, intensity, jitter, tenseness, mean spectral energy (e.g., Fuller, Horii, & Conner, 1989; Grunau & Craig, 1987; Grunau et al., 1990; Porter et al., 1986; Zeskind & Lester, 1978). These studies have used different noxious stimuli to elicit the cry response including pin pricks, rubber band snaps, skin pinch, heel lance, injections, and circumcisions (Table 3.1). Most of the neonate samples included only well neonates; the tranferability of these find-ings to ill infants in questionable.

The research of Fisichelli and colleagues (1974) suggests that the character of the cry reactivity during the first year of life is mainly a function of age or maturation of the neurological system. In the neonatal period, the cry reactivity, depressed at five hours of age, increases by two days of age and then remains stable throughout the neonatal period. In all but two studies reviewed (Bosma et al., 1965; Fisichelli et al., 1974), the neonates were between two hours and four days old; thus their age across the studies was in the very early neonatal period.

Unlike preterm neonates, most term neonates have a cry response under aversive situations. The cry of term neonates is greater with invasive procedures than with noninvasive procedures (Owens & Todt, 1984). The latency of the cry is shorter (Grunau et al., 1990) but the cry is longer in duration (Grunau et al., 1990; Porter et al., 1986) with procedures that are more invasive. Often cry corres-ponds with body movements and/or facial expression, suggesting a greater behavioral arousal (e.g., Franck, 1986; Rich et al., 1974). However, Grunau et al. (1990) concluded that the lack of a correlation between facial activity and cry acoustics suggested that these response modes operate differently. Mea-surement approaches for cry and facial expression may account for these differences. Rich et al. (1974) recorded the presence of cry and facial grimace. Grunau et al. (1990) used more sophisticated methods to interpret the facial and cry parameters; they measured facial activity with the Neonatal Facial Coding System (Grunau & Craig, 1987) and cry acoustics (e.g., fundamental frequency {pitch}, melody, jitter, and phonation) with spectrographs.

Through spectrographic analysis, cries associated with the most invasive aspects of circum-cision (e.g., clamping and cutting) were higher in pitch (Fuller et al., 1989; Holve et al., 1983; Porter et al., 1986) and more tense (Fuller et al., 1989) with fewer harmonics (Porter et al., 1986). Both Fuller et al. (1989) and Porter et al. (1986) stated that obser-vers or trained listeners can identify such cries. Porter et al. (1986) found that external judges identi-

Zeskind and Lester (1978) compared cries of low and high risk (secondary to maternal and parturitional factors) neonates. A snap from a rubber band elicited the cries. Cries from the high risk neonates were harder to elicit resulting in a longer latency period. Like preterm infants, the high risk neonates cried less but with a higher pitch. Zeskind and Lester (1978) showed that observers could discrim-inate between cries of these low and high risk neo-nates. Cries from high risk neonates were urgent, grating, arousing, sick, piercing, discomforting, aver-sive, and distressing.

Much remains unknown about the cry of the neonate. Prevailing issues are whether a pain sig-nature exists (Johnston & Strada, 1986) and how severity of illness alters the cry response. However, not all infants cry in response to aversive stimuli. As such, cry lacks specificity as a measure of pain and is only a probabilistic sign of pain (Grunau et al., 1990).

Facial activity is a promising measure of pain. Whether the observed grimace (e.g., Franck, 1986; Rich et al., 1974) is sufficient for determining pain is an issue. Based on the work of Craig and Patrick (1985) and Ekman and Friesen (1971), Grunau and Craig (1987) developed the Neonatal Facial Coding System. Comparison of facial expres-sions elicited by a heel rub and a heel lance revealed five parameters consistent with a pain expression: brow contraction, eye squeeze, naso-labial furrow, open mouth, and taut tongue (Grunau & Craig, 1987). Subsequently, Grunau et al. (1990) compared the facial activity across three situations including one invasive procedure. Facial activity was greater for the invasive procedure but tongue action was the most discriminatory: taut tongue was more evident with the invasive procedure while tongue protrusion occurred with the noninvasive situations. Thus, facial grimace with a taut tongue may be a sensitive pain expression.

Limb movement is a response to aversive stimuli such as pin pricks (Rich et al., 1974) and heel lance (Franck, 1986). Franck (1986) used a photogrammetric technique to measure the movement of the legs following heel lance. Like Rich et al. (1974), Franck (1986) found that the neonates immediately withdrew both legs and then cried. Unique to Franck's study was the quantification of gross motor reaction time, velocity of leg movements, number of leg movements, and number of movements directed toward the stimulus. The small sample (*n* = 10) precluded any normative data generation for these motor responses to aversive stimuli. Crying accompanied facial grimacing and movement of all extremities.

The physiological response to aversive stimuli includes increases in *heart rate* (Maxwell, Yaster, Wetzel, & Niebyl, 1987; Owens & Todt, 1984; Rawlings, Miller, & Engel, 1980; Wiliamson & Williamson, 1983), *respiratory rate* (Brown, 1987; Rawlings et al., 1980), *systolic blood pressure* (Brown, 1987), and *cortisol and cortisone* (Gunnar, Fisch, Korsvik, & Donhowe, 1981; Talbert, Kraybill, & Potter, 1976; Williamson & Evans, 1986). Oxygen saturation decreased (Maxwell et al., 1987, Rawlings et al., 1980; Wiliamson & Williamson, 1983) and increased (Brown, 1987) in response to aversive stimuli. Owens and Todt (1984) noted the potential interplay between physiological and behavioral responses by reporting that heart rate and cry covary. The limitation for obtaining some of these physiological measures is that stress-inducing invasive procedures are necessary and stress per se, in the absence of nociception, may produce these responses.

Despite the concern that procedures cause pain in neonates, few studies have focused on preventing or alleviating the pain. A few studies suggested that topical anesthetics are promising. A topical anesthetic, amethocaine, reduced pain (rated on a four-point scale by nursing and medical staff) in 82% of the infants (0 to 2 years) undergoing venipunctures (Woolfson, McCafferty, & Boston, 1990). The topical application of lidocaine prior to circumcision altered heart rate, duration of crying, and severity of response but not respiratory rate or oxygen saturation (Mudge & Younger, 1989).

The use of dorsal penile nerve blocks altered physiological and behavioral responses to circumcisions (Dixon, Snyder, Holve, & Bromberger, 1984; Holve et al., 1983; Maxwell et al., 1987; Stang, Gunnar, Snellman, Condon, & Kestenbaum, 1988; Wiliamson & Williamson, 1983). Neonates with the penile blocks exhibited less crying (Holve et al., 1983; Wiliamson & Williamson, 1983), were more quiet (Maxwell et al., 1987), were less irritable (Dixon et al., 1984), were more attentive to stimuli following the circumcision (Dixon et al., 1984), and had a greater ability to quiet themselves when disturbed (Dixon et al., 1984). Although the findings in two studies that measured heart rate are inconsistent (Maxwell et al., 1987; Wiliamson & Williamson, 1983), the findings supported the efficacy of the nerve block. Wiliamson and Williamson (1983) found attenuated increases in heart rate in the neonates with the penile blocks and Maxwell et al. (1987) found heart rate and blood pressure unchanged from baseline levels. Oxygen saturation was higher in infants with penile blocks (Maxwell et al., 1987; Wiliamson & Williamson, 1983). The nerve block did not affect cortisol levels (Williamson & Evans, 1986). One complication, a small unilateral hematoma, occurred with the administration of 61 nerve blocks (Holve et al., 1983). Overall, these findings suggest that the nerve block is an effective approach to managing the pain associated with circumcision even though nerve blocks require injections. Side effects of nerve blocks need further study.

Campos (1989) examined the use of pacifiers and swaddling with neonates undergoing heel lance. Pacifiers effectively decreased the behavioral (crying) and physiological (heart rate) arousal from heel lance. Removal of the pacifier after the heel lance resulted in crying and increased heart rate. Swaddling produced modest decreases in heart rate but did not alter crying behavior. Removal from the swaddling condition resulted in minimal decreases in heart rate and crying. The pacifier was more effective than swaddling in soothing the neonate from pain associated with heel stick. Others, however, did not find that pacifier alone or in combination with classical music and intrauterine sounds effectively reduced pain associated with circumcisions (Marchette, Main, & Redick,, 1989; Marchette, Main, Redick, Bagg, & Leatherland, 1991). The use of a pacifier plus sucrose was more effective than a pacifier plus water in reducing crying during heel lance and circumcision (Blass & Hoffmeyer, 1991). This finding is preliminary; further study is needed to demonstrate the efficacy of surcrose for neonates undergoing invasive procedures.

The assessment and management of the immediate pain response reveals that neonates respond behaviorally and physiologically to various pain stimuli. Measurement strategies, however, are under development and are not clinically applicable. Nerve blocks for circumcision pain are effective, but this finding should not preclude the search for a less invasive strategy for minimizing pain. The use of comforting strategies (pacifiers and swaddling) is promising but needs further research.

Like the response of preterm neonates, the *established pain response* in term neonates is understudied. No tools are available to measure established pain in the term neonates.

Anand and colleagues (Anand, Brown, Bloom, & Aynsley-Green, 1985; Anand, Brown, Causon, Christofides, Bloom, & Aynsley-Green, 1985) showed that anesthetized term neonates ($n$ = 23 & 26, respectively) are at risk for problems from hyperglycemia up to 24 hours postoperatively. (See discussion under Stress Response).

Emde, Harmon, Metcalf, Koenig, and Wagonfeld (1971) focused on longer term effects of circumcision by studying the amount of REM and non-REM sleep during the night after the procedure. They found that circumcised neonates spent more time in non-REM sleep than did noncircumcised neonates. They hypothesized that the non-REM sleep allows for the growth and repair of body tissues. Anders and Chalemian (1974), however, did not replicate these findings. Neither of these studies examined whether anesthesia such as a nerve block would alter the sleep pattern post-circumcision.

Research on the management of established pain in neonates is extremely limited. Opioids are considered the mainstay for treatment of postoperative pain (Berde, 1989); however, the use of opioids in neonates is recommended in reduced doses (Berde, 1989; Tyler & Krane, 1989a, 1989b). Koren, Butt, Chinyanga, Soldin, Tan, and Pape (1985) examined the pharmacokinetics and safety of morphine infusion in newborns postoperatively. Two neonates on higher doses of morphine developed gen-eralized seizures. Because neonates metabolize opioids differently (Way, Costley, & Way, 1965) and plasma clearance is slower, Koren and colleagues (1985) recommended morphine be provided to neo-nates in reduced doses.

Studies on fentanyl suggested that this drug is effective and safe intraoperatively. Fentanyl provides adequate anesthesia with few hemodynamic changes (Yaster, 1987) but its clearance is decreased in neonates (Gauntlett, Fisher, Hertzka, Kuhls, Spellman, &

Rudolph, 1988). Intraoperative sufen-tanil effectively modifies the stress response of neonates undergoing cardiac surgery (Anand, Phil, Carr, & Hickey, 1987; Anand, Phil, & Hickey, 1987). However, as with fentanyl, the clearance rate for neonates is decreased (Greeley & de Bruijn, 1988; Greeley, de Bruijn, & Davis, 1987).

The research on pain and neonates does not provide sufficient information on how to assess and manage the established pain response. The lack of reliable, valid, and sensitive measurement strategies inhibits the study of pain management. Needed are studies that focus on (a) use of opioids and regional anesthesia and analgesia techniques, (b) risks and benefits of medicating neonates on an acute basis, (c) use of nonpharmacologic approaches, and (d) risks associated with unresolved acute and procedural pain.

***Infants***

The <u>*immediate pain response*</u> in infants (one to twelve months) consists of behavioral and physiological arousal. Behavioral arousal includes crying, changes in facial expression, increased body movement, and negative behavior. Increases in heart and respiration rates and blood pressure signal a physiological arousal. As with the neonate, the emphasis of research is on the behavioral response, particularly crying.

According to Fisichelli and colleagues (1974), crying reactivity established at two days of age remains stable until about three months when cry-ing reactivity and crying duration diminish. After three months, the number of infants not crying after a rubber band snap increased through the remainder of the first year of life. These findings suggested that the characteristics of the cry may differ between younger infants (one to three months) and older in-fants (three to twelve months). However, research on infant crying in response to pain has not focused on differences within the first year of life.

Because the diphtheria-pertussis-tetanus (DPT) injection is a common experience for infants, all research (except that by Fisichelli and colleagues, 1974) used this intramuscular injection as the stimulus to characterize the infant's immediate pain response (Table 3.2). The common times for measuring cry was at two, four, and six months when the DPT in-jection is given routinely. Crying and other vocaliza-tions (e.g., screaming) were the most common reac-tions to an injection (Craig, McMahon, Morison, & Zaskow, 1984; Dale, 1986; Dale, 1989); however, the duration of crying varied across infants (Dale, 1986).

Acoustic parameters of a cry induced by an injection differ from cries indicating *hunger* (Brockway-Fuller, 1984; Fuller & Horii, 1986; Fuller & Horii, 1988, Fuller et al.,1989), *fussiness* (Brockway-Fuller, 1984; Fuller & Horii, 1986, 1988; Fuller et al.,1989), *fear* (Johnston & O'Shaughnessy, 1988), and *anger* (Johnston & O'Shaughnessy, 1988). Ful-ler and colleagues also distinguished the pain cry from cooing through acoustic parameters. The acou-stic parameters associated with pain cries, however, differed by research group. In the Fuller studies, characteristics of the pain cry were a higher pitch (as estimated by fundamental frequency) and greater tenseness (as estimated by mean spectral energy) while Johnston and O'Shaughnessy (1988) and John-ston and Strada (1986) reported higher frequency and higher intensity of the second formant, higher pitch, more dysphonation, and a greater proportion of flat or falling melodies for pain cries. A high pitch is the common finding across these studies but Johnston and Strada (1986) cautioned that pitch is highly variable, particularly in initial cries.

The infant's immediate response to injections also involves facial movement (Craig et al., 1984; Dale, 1986, 1989; Izard, Hembree, Dougherty, & Spizzirri, 1983; Izard, Huebner, Risser, McGinnes, & Dougherty, 1980; Johnston & Strada, 1986). The facial expression associated with injections was distinguishable from other emotion expressions such as joy, surprise, contempt, and fear (Izard et al., 1980). The difficult distinction is between pain and anger. Izard and colleagues (1983) found that most infants displayed a facial expression of physical distress; however, an age-related trend emerged. Facial expressions of physical distress decreased and anger expressions increased with age.

Dale (1986, 1989) and Johnston and Strada (1986) concurred on their descriptions of the pain expression for infants from six weeks to six months. Johnston and Strada (1986) provided this detailed elaboration: brows lowered and drawn together with a bulge between the brows, the nasal root broadened and bulged, eye fissure scourged with eyes tightly closed, and an angular, squarish mouth. The facial expression shows the least variability for infants younger than six months when compared with other measures (e.g., cry, body movement, and heart rate).

Body movements may occur as part of the infant's response to pain. Craig et al. (1984) noted that limb movement was infrequent while Dale (1986) described a wide repertoire of body movements including those of limbs. The findings of Johnston and Strada (1986) suggested that body movements are probably infrequent but two to four month old infants display a pattern of body movements beginning with rigidity of the body and limbs at the time of injection, followed by residual rigidity and some thrashing, and finally return to normal body posturing and movements. The inconsistencies noted in body movements suggest that the estimation of pain through body movements is highly suspect.

Another important behavior is vigilance. The findings from Craig et al. (1984) suggested that vigilant behavior such as tracking the nurse and watching the injection increases with age. The rela-tionship between vigilance and pain, however, is not established.

As in neonatal studies, heart rate increased with aversive stimuli (Dale, 1986). However, Johnston and Strada (1986) observed an immediate episode of bradycardia followed by a rise in heart rate. This finding, however, may be the result of the time when heart rate was measured (i.e., within six seconds of the injection versus 15-30 seconds) and not differences in the infant samples.

Tools to measure the immediate pain res-ponse in infants are not yet available for clinical practice. The Infant Pain Behavior Rating Scale (Craig et al., 1984) is a multidimensional scale that focuses on vocalizations, facial expression with emphasis on the orientation of eyes, posturing of the torso, protection of affected limb, and limb move-ment. Interrater reliability estimates were satisfactory (> .70) only for four of twelve subscales. No infor-mation on validity is available.

Management for immediate pain experienced by infants is not well documented. Typically, a study on the pharmacologic treatment of pain includes a small number of children ranging in age from infancy through adolescence. Use of this age range creates several problems unless the study presented a developmental analysis of the findings. From a physiological perspective, the pharmacokinetics of drugs may differ until the infant is three to six months. From a measurement perspective, studies involving preverbal and verbal children need to approach measurement of pain differently. No one tool is appropriate across these developmental periods, especially considering the differences in behavioral competency. Too often investigators inappropriately apply the same strategy across children of diverse ages and developmental abilities. Some investigators use an observer report of pain on an intensity scale, an approach lacking reliability and validity estimates. Thus, conclusions about the effects of pharmacologic agents for infants may be erroneous.

To prevent overgeneralization, only studies that met at least one of two conditions were appro-priate for inclusion in this report on infants. The conditions were: (a) the age of study infants fell within one standard deviation of the mean age for the total sample and (b) the study provided posthoc analysis of findings from a developmental perspective.

Only one study focused on the treatment of immediate pain. Woolfson et al. (1990) found that amethocaine, a topical anesthetic, was a safe and effective alternative for pain associated with veni-punctures. Few (4.4%) adverse reactions (i.e., slight transient erythema) occurred but infants (0 to 2 years) benefited less from amethocaine than did older children. This finding, however, may reflect the difficulty of measuring pain in infants rather than a difference in benefit.

Studies on nonpharmacologic approaches are few. Campos (1989) found that swaddling and pacifiers were effective in reducing heart rate and crying associated with intramuscular injections in two- month old infants. Caire and Erickson (1986) used relaxation audiotape and an audiotape of lullabies and nursery rhymes for infants undergoing cardiac catheterizations. Although the tapes were effective in distracting the infants and as such are promising, these findings need replication secondary to the small sample (*n* = 5) and inadequate measurement strate-gies for perceived benefit and patient anxiety.

The infant response to immediate pain is very much understudied. Studies have focused primarily on infants under six months. No reliable and valid measurement strategies are available for clinical practice. Few studies focus on the relief of immediate pain through pharmacologic agents and nonpharmacologic strategies.

The *established pain response* is addressed in few studies. Mills (1989a, 1989b) observed the behavior of infants with surgical wounds, fractures, and burns over three occasions. (These observation periods occurred when the infant had not received analgesics for at least four hours). Behaviors were categorized according to age (in four three-month intervals). Motor responses in the first year changed dramatically from vague non-specific movements to controlled intentional movements. Communication in the early months was primarily through intermittent or sustained crying and it changed to anticipatory cries and use of language. Facial expressions, pri-marily grimaces or frowns, in the early months changed to expressions of more specific emotions such as surprise, fear, sadness, anger, and vigilance. These findings are preliminary and need replication.

Tools are needed for measuring the established pain response. One available tool is the Clini-cal Scoring System for Measurement of Postoperative Pain (Attia, Amiel-Tison, Mayer, Shnider, & Barrier, 1987; Barrier, Attia, Mayer, Amiel-Tison, & Shnider, 1989). The items on this scale associate pain with behavioral arousal (e.g., ability to sleep, marked facial expression, screaming, exaggerated body movements, and hypertonicity) and with social responses (e.g., inability to console and lack of eye contact). A high score is associated with a pain-free status. Although preliminary research suggested a difference in pain scores between medicated and non-medicated infants (one to seven months), the small sample size (*n* = 23) precludes generalization of the findings. This tool needs further psychometric eval-uation before widespread use.

Several studies on pharmacologic strategies to prevent or alleviate established pain included infants; however, few studies met the conditions sta-ted above for inclusion in this report: (a) the age of infancy was within on standard deviation of the mean age of the sample; and (b) a posthoc analysis of findings from a developmental perspective was inclu-ded. In most studies, the age of the study infants was more than one standard deviation below the mean. Most of these studies did not attend to differ-ences related to developmental stages in the measure-ment of responses, the analyses or the discussion.

Regional anesthesia was the focus of six studies. Three studies examined anesthesia/analgesia through the caudal route (Eyres, Bishop, Oppenheim, & Brown, 1983; McGown, 1982; Rasch, Webster, Pollard, & Gurkowski, 1990). McGown (1982) reported on the use of caudal analgesia in 500 children, including 142 infants. Based on a low failure rate, McGown (1982) concluded that the caudal approach using lignocaine was effective in providing analgesia for upper abdominal surgery. Eyres et al. (1983) examined plasma levels of bupivacaine delivered through the caudal epidural route. Although plasma levels in infants under one year tended to be higher than those of older children, they did not differ statistically. Rasch et al. (1990) studied the effectiveness of lumbar and thoracic epi-dural analgesia (using morphine) through the caudal approach for relief of pain associated with gastro-intestinal, genitourinary, and thoracic procedures. According to Rasch and colleagues (1990), analgesia was adequate but a definition of "adequate" was lack-ing. Of 21 infants, two experienced complications; the most serious complication, an apneic episode, re-versed without further problems. These studies suggested that the caudal route using bupivacaine or morphine are safe and potentially effective approach-es to preventing postoperative pain in infants.

Ecoffey, Dubousset, and Samii (1986) performed epidural anesthesia (using bupivacaine) through lumbar and thoracic routes on infants under-going urological procedures and surgery for biliary atresia. The lumbar and thoracic routes were feasible and provided effective analgesia for infants as young as three months. The thoracic route for epidural anesthesia with bupivacaine was effective for infants over six months of age who suffered from respiratory disabilities (Meignier, Souron, & Le Neel, 1983).

Murat, Delleur, Esteve, Egu, Raynaud, and Saint-Maurice (1987) compared continuous extradural anesthesia using bupivacaine with and without adrenaline. For children from two days to two years, the duration of the blocks with adrenaline was signifi-cantly longer. The extradural catheter remained in place until no injections had been made for 18 hours and the child appeared pain free. But the deter-mination of the pain-free status was not discussed. No complications occurred with the block adminis-tration. Both blocks were effective for pain relief but the addition of adrenaline potentiated the duration of effect.

Studies on opioids suggested that morphine is safe and effective for infants over six months (Bray, 1983; Olkkola, Maunuksela, Korpela, & Rosenberg, 1988). Bray (1983) noted that infants under six months developed irregular breathing patterns that were dose-related. The pharmaco-kinetics of intravenous morphine were different for infants younger than three months. The patterns for pharmacokinetics in older infants were comparable to those of adults (Olkkola et al., 1988). Hertzka, Gauntlett, Fisher, and Spellman (1989) reported that infants older than three months were not sensitive to fentanyl-induced ventilatory depression but questioned whether younger infants were. Although Greeley et al. (1987) found that the pharmacokinetics of sufen-tanil for infants and toddlers (one to 24 months) were similar to those for older children and adolescents, this study included only two infants under six months. A subsequent study focused on the pharm-acokinetics of sufentanil with neonates. Although the sample was small, Greeley and de Bruijn (1988, p. 90) concluded that the "variability in clearance...in the early neonatal period makes dosing of this drug and its duration of anesthetic response unpredictable." These studies suggested that infants under six months metabolize opioids differently.

Studies on established pain in infants are limited in number. Of great concern is the lack of reliable and valid measures for pain. The lack of such measures definitely affects the confidence in the pharmacologic intervention studies which determine effectiveness by the degree of pain relief. No studies focused on nonpharmacological strategies.

### *Toddlers*

The *immediate pain response* has been studied in regard to intramuscular injections and bone marrow aspirations. Craig et al. (1984) found that toddlers from 12 to 24 months cried about the same as infants, but that they screamed less and began to use language and more goal-directed movements in response to intramuscular injections. They also exhibited anticipatory distress prior to the injection. According to Izard et al. (1983), toddlers responded with facial expressions of anger rather than physical distress. Frequent behaviors associated with bone marrow aspiration included crying and screaming (Katz, Kellerman, & Siegel, 1980).

Pharmacologic studies addressed the immediate pain response to venipunctures and circumcisions. Topical anesthetics, EMLA and amethocaine, were effective in reducing pain accompanying venepuncture (Hopkins, Buckley, & Bush, 1988; Woolfson et al., 1990). No serious side effects occurred with either anesthetic.

Although toddlers usually have generalized anesthesia for circumcisions, studies on penile blocks and topical anesthetics have been conducted with them. The dorsal penile block is an alternative for pain associated with circumcision (Dalens, Vanneuville, & Dechelotte, 1989; Soliman & Tremblay, 1978). The block reduced the immediate response and affected the established response. Dalens et al. (1989) found bupivacaine provided longer duration than lidocaine. More agitation occurred in children not receiving the block (Soliman & Tremblay, 1978). Tree-Trakarn and Piraya-varaporn (1985) compared the penile block, morphine, and three forms of the topical anesthetic lidocaine (i.e., spray, ointment, and jelly) and found that all approaches were equally effective in ablating the immediate pain response. The duration of the effect lasted four to five hours, thus altering the established pain response.

Nonpharmacologic strategies include the use of relaxation tapes or taped music or stories, play therapy, and child participation and control. Caire and Erickson (1986) found that the effectiveness of the tapes was highly variable for toddlers. Toddlers preferred story tapes but tapes were of little benefit. Measurement problems, however, plagued this study. Play therapy was useful in helping toddlers express their concerns regarding invasive procedures (Ellerton, Caty, & Ritchie, 1985). Play with invasive equipment predominated among the children, suggest-ing that children needed an opportunity to master their concerns regarding intrusive medical proce-dures. Providing opportunities for toddlers to exhibit control and autonomy during burn care is another approach to helping toddlers as young as 18 months, in their mastery over intrusion (Kavanagh, 1983a, 1983b). Negative behavior associated with dressing changes significantly decreased for children who par-ticipated in their care. Distraction with television programs was not effective in reducing children's response to dental treatment (Venham, Goldstein, Gaulin-Kremer, Peteros, Cohan, & Fairbanks, 1981).

Studies related to immediate pain for tod-dlers lack adequate approaches to measuring pain. While a few studies have documented the efficacy of various interventions for ablating pain associated with procedures, the body of literature is small and results are preliminary. Research is needed on the develop-ment of assessment tools and the efficacy of pharmacological and nonpharmacological approaches. Promising nonpharmacological strategies include play therapy and increased child participation.

The *established pain response* for toddlers in the early postoperative period is characterized by restless, guarding, contacting, and grimacing move-ments; vocalizations such as crying, groaning, and whining; and verbalizations (Taylor, 1983). Al-though movements are common in the first post-operative hour, they decrease when toddlers realize that movement is related to pain. By the second hour movements become more controlled and protective. Similar patterns are evident for vocalizations except whining, which increases across time. Observations of toddlers in pain revealed that they tend to use vocalizations more than body movements or facial expression (Mills, 1989a, 1989b).

Tools to measure pain in toddlers include the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (McGrath, Johnson, Goodman, Schil-linger, Dunn, & Chapman, 1985) and the Gustave-Roussy Child Pain Scale (Gauvain-Piquard, Rodary, Rezvani, & Lemerle, 1987; Gauvain-Piquard, personal communication, April, 1991). The development of the CHEOPS was based on recovery room nurses' descriptions of children's behavior immediately after surgery. Recently, however, the tool yielded flat scores for preschool children post-operatively, raising concerns about its validity (Beyer, McGrath, & Berde, 1990). In consideration of Taylor's findings, the behaviors described by the recovery room nurses were not generalizable beyond the immediate recovery room period.

Although the Gustave-Roussy Child Pain Scale was designed to measure pain experienced by children with cancer, the behaviors on this scale are highly consistent with Taylor's descriptions of post-operative behavior, e.g., protection of painful areas, control exerted when moved, and antalgic rest posi-tion. The tool has preliminary evidence for relia-bility, validity, and sensitivity but only with the cancer population.

Often tools used in pharmacologic studies are constructed without consideration for their reliability, validity, and sensitivity properties or for their age appropriateness. One example is the use of tools such as the Pain/Discomfort Scale (Hannallah, Broadman, Belman, Abramowitz, & Epstein, 1987). The items on the scale are of concern. An increase in arterial blood pressure is considered indicative of pain but this indicator has yet to be substantiated. The criteria for the observations of crying and movement are not consistent with detailed observa-tions of toddlers postoperatively (Mills, 1989a, 1989b; Taylor, 1983). Tools such as this may yield scores of no pain, suggesting that the interventions were effective when they may not have been.

Another example is to have toddlers provide self-reports of pain even though research has yet to demonstrate the reliability and validity of self-report pain ratings for children under four (McGrath, 1990). A third example is to have health care providers (e.g., nurses) rate the amount of pain on visual analogue scales often without behavioral or physio-logical criteria. Again research has not substantiated that measures from an observer using a visual ana-logue scale are reliable and valid. A fourth example is the measurement of the time lapse between the ini-tiation of the anesthesia or the analgesia and the first subsequent administration of an analgesic. This approach is likely to be error-laden considering the substantial body of literature on the infrequent use of analgesics with the preverbal child. Whether an analgesic is administered is not an accurate measure-ment of onset of pain. The final example is the use of different measurement approaches for children in different age groups (e.g., other report for toddlers and self-report for children older than three) and combination of the results as though the strategies measured the same constructs and had similar measurement errors. These measurement problems seriously compromise the interpretability of pharma-cologic studies and restrict the findings to preliminary or tentative.

Review of pharmacologic studies revealed several foci: *methods for drug administration* (e.g., Dalens et al., 1989; McNichol, 1985, 1986; Shelly & Park, 1987; White, Harrison, Richmond, Proctor, & Curran, 1983; Yeoman, Cooke, & Hain, 1983), *types of drugs* (e.g., Forestner, 1988; Ginsberg & Gerber, 1969; Krane, Jacobson, Lynn, Parrot, & Tyler, 1987; Murat et al., 1987; Tree-Trakarn & Pirayavaraporn, 1985), *dosages* (e.g., Krane, Tyler, & Jacobson, 1989; Wolf, Valley, Fear, Roy, & Lerman, 1988), *timing of administration* (e.g., Rice, Pudimat, & Hannallal, 1990) and *pharmacokinetics* (e.g., Attia, Ecoffey, Sandouk, Gross, & Samii, 1986; Dahlstrom, Bolme, Feychting, Noack, & Paalzow, 1979; Murat, Walker, Esteve, Nahoul, & Saint-Maurice, 1988; Takasaki, 1984).

Most studies addressed regional blockades; for example, *caudal epidural with opioids* (e.g., Jensen, 1981; Krane, 1988; Krane et al., 1989; Krane et al., 1987; Rasch et al., 1990; Rosen & Rosen, 1989), *caudal epidural with local anesthetics* (e.g., Ecoffey et al., 1986; Eyres et al., 1983; Fell, Derrington, Taylor, & Wandless, 1988; Jensen, 1981; Malviya, Fear, Roy, & Lerman, 1988; Meignier et al., 1983; Payne, Heydenrych, Martins, & Samuels, 1987; Rice et al., 1990; Soliman, Ansara, & Laberge; 1978; Warner, Kunkel, Offord, Atchinson, & Dawson, 1987; Wolf et al., 1988), *wound infiltration* (e.g., Fell et al., 1988; Langer, Shandling, & Rosenberg, 1987; Reid, Harris, Phillips, Barker, Pereira, & Bennett, 1987), *illioinguinal* (e.g., Reid et al., 1987; Shandling & Steward, 1980; Smith & Jones, 1982), *dorsal penile nerve* (e.g., Dalens et al., 1989, Soliman & Tremblay, 1978; Tree-Trakarn & Pirayavaraporn, 1985), *sacral* (e.g., Busoni & Sarti, 1987) and *sciatic* (e.g., McNichol, 1985, 1986).

Fewer studies have focused on the use of opioids: *intramuscular morphine* (Bray, 1983; Tree-Trakarn & Pirayavaraporn, 1985; Wandless, 1987), *intermittent intravenous morphine* (Krane et al., 1987; Maunuksela, Korpela, & Olkkola, 1988; Olkkola et al., 1988; Shelly & Park, 1987), *continuous infusion of morphine or other opioids* (e.g., Bray, 1983; Dilworth & MacKellar, 1987), *intrathecal morphine* (Tobias, Deshpande, Wetzel, Facker, Maxwell, & Solca, 1990), *buprenorphine* (Maunuksela et al., 1988), *fentanyl* (Hertzka et al., 1989), and *sufentanil* (Greeley & de Bruijn, 1988). Other drugs studied include two *nonsteroidal anti-inflammatory agents*, rectal diclofenac (Moores, Wandless, & Fell, 1990) and indomethacin (Maunuksela, Olkkola, & Korpela, 1988); *pentazocine* (Waterworth, 1974); and *premedi-cation drug combinations* (Brzustowicz, Nelson, Betts, Rosenberry, & Swedlow, 1984). With so few studies of these drugs, conclusions concerning their effectiveness is premature.

Toddlers have a better postoperative course when they receive analgesia. Most of the previously mentioned studies documented the efficacy of the various pharmacologic strategies. Regional blockades were effective in reducing or eliminating pain. Analgesics administered *pro re nata* (PRN) did not effectively reduce pain. Studies on round-the-clock administration are needed.

Respiratory depression occurred infrequently with the administration of opioids through blockades, infusions, and intermittent intravenous and intramuscular routes. Reports of complications were rare. The most frequent side effects were nausea, vomiting, pruritus, and delayed micturition.

Only one study discussed the potential reduction of costs associated with adequate pain relief. Fleming and Sarafian (1977) found that children who had an intercostal nerve block required fewer hospital days. More research is needed to demonstrate whether postoperative pain relief leads to better outcomes such as cost savings.

Established pain in toddlers has been studied more extensively than in preterm and term neonates and infants especially from a pharmacologic perspective. The Gustave-Roussy Child Pain Scale is strong-ly promising as a reliable, valid, and sensitive measure for established pain in toddlers. However, tools used to measure the effectiveness of pharma-cologic strategies often lack psychometric evidence and may be developmentally and contexually inappro-priate. This problem limits the interpretability of the pharmacologic studies. If these tools yielded accurate information, most pharmacologic approaches would be effective. However, many pharmacologic issues have not been addressed: efficacy of nonsteroidal anti-inflammatory drugs (NSAIDS), effectiveness of routine administration of opioids and NSAIDS, com-parison of continuous infusions versus round-the-clock intravenous boluses, use of epidural analgesia, occurrence and treatment of break-through pain, and cost effectiveness of high technological procedures versus conventional approaches. Studies focus on the use of high technological rather than conventional approaches to pain management, establishing com-parable efficacy between these approaches could prove to be cost effective. Nonpharmacologic stra-tegies for toddlers have received little research attention.

### *Assessment and Management: Other Pain*

Few studies have focused on pain other than acute or procedural. The purpose of including vis-ceral, deep somatic, and neuropathic pain is to de-monstrate the paucity of research.

Only one assessment tool for pain other than cutaneous has been developed for preverbal children. The Gustave-Roussy Child Pain Scale (Gauvain-Piquard et al., 1987; Gauvain-Piquard, personal communication, April, 1991), designed to measure pain experienced by children with cancer, has evi-dence for reliability, validity, and sensitivity.

Others have attempted to identify pain reponses for children experiencing pain other than cutaneous. Jones (1989) identified signs that nurses interpret as pain in newborns, the signs most com-monly associated with pain were fussiness, crying, and grimacing, but these signs are not specific for pain. For example, these signs could indicate infant irritability (Budreau & Kleiber, 1991) or agitation (Gordin, 1990). Thus, a need exists for develop-mentally appropriate tools to measure pain other than cutaneous in preverbal children.

Pain is associated with common childhood illnesses but few studies have addressed the assess-ment or treatment of this pain. For example, otitis media can be extremely painful. Pukander (1983) reported that 74% of children with acute otitis media had earaches. Hayden and Schwartz (1985) conclu-ded that preverbal children exhibited less pain with otitis media than did older children. Their approach to determining pain, however, lacked psychometric information.

Colic is sometimes referred to as a pain syndrome of infancy (Geertsma & Hyams, 1989) but whether it is a pain syndrome is controversial (Pinyerd & Zipf, 1989). Several causes have been attributed to colic (e.g., malabsorption and gas func-tion, gastrointestinal allergy, and gastrointestinal reflux). Keefe (1988) identified colic as an irritable infant syndrome. Recent research by Keefe and and Fuller (1992) suggested that the spectrographic analy-sis of the cries associated with colic differ from those associated with cutaneous pain (e.g., injections and circumcisions). Current evidence on whether colic is a pain syndrome is inconclusive.

Pain is associated with other conditions such as sickle cell disease and cancer. Studies on sickle cell disease stressed the importance of pharmacologic treatment during the vaso-occlusive crisis (Morrison & Vedro, 1989; Sartori, Gordon, & Darbyshire, 1990; Shapiro, 1989) but assessment of pain in the preverbal child was not discussed. In a case study of an infant with advanced neuroblastoma, Berde, Fischel, Filardi, Coe, Grier, and Bernstein (1989, p. 221) commented that when the infant was touched or turned, "he responded with crying, clenching of fists, tachycardia, mottling, and generalized stiffening," signs potentially associated with pain.

Pharmacologic treatment is similar to that for postoperative pain. For conditions such as otitis media, acetaminophen is the common approach. A topical anesthetic applied to the ear may help alleviate the pain. Morphine is appropriate for severe pain associated with cancer and sickle cell disease (e.g., Berde et al., 1989; Lynn & Slattery, 1987; Shapiro, 1989).

Nonpharmacologic approaches are not well documented. Triplett and Arneson (1979) demonstrated the efficacy of tactile and verbal interventions for crying infants. Crying may have occurred for several reasons including hunger and pain. If crying indi-cated pain, then this is the only study conducted on nonpharmacological strategies for pain related to gastrointestinal problems, central nervous system disorders, and upper respiratory conditions. Tactile comfort included stroking, patting, rocking, and holding while verbal comfort included talking, hum-ming, singing, or making soothing noises. Simul-taneous verbal and tactile interventions were effective in quieting a crying toddler. Verbal interventions were more effective for children who were older than 12 months.

The research on pain other than cutaneous is a weak, fragmented body of literature. Research is needed on the prevalence of pain, the measurement of pain, and its treatment.

### *Parent's Role*

Few studies have emphasized the parent's role with preverbal children. Parental presence is especially important during induction of anesthesia (Hannalah & Rosales, 1983; Schofield & White, 1989; Vernon, Foley, & Schulman, 1967). Toddlers tend to protest when mothers leave during immuniza-tion procedures but they also tend to behave more negatively when mothers are present during the injec-tion (Shaw & Routh, 1982). Potentially, the presence of parents promotes toddlers' expression of feelings.

Separation from mother is one of the most difficult situations for hospitalized children. Mothers help them by comforting them and providing accurate information, physical care or protection, and diversion (Caty, Ritchie, & Ellerton, 1989). While these studies provide preliminary information about the parental role, the effect of parental participation on pain experienced by preverbal children lacks adequate documentation.

## Research Needs and Opportunities

The state of the science regarding preverbal children and pain is in the early stage of development. Few studies were conducted before the mid 1980s. Hence, the young science provides direc-tion for continued research efforts but does not provide an adequate basis for clinical practice. Research needs and opportunities are evident in several areas: physiological processing of nocicep-tion and short and long term physiological effects of untreated pain; response to cutaneous, visceral, deep somatic, and neuropathic pain; measurement of pain; pharmacokinetics and pharmacodynamics of anal-gesics, anesthesia, and adjuvant drugs in preverbal children; management of pain; role of parents; and integration of pain care into health care delivery systems. Further, researchers must use more com-plex multivariate designs to capture the multi-dimensionality of the pain phenomenon.

### *Physiological Research*

Research on the neural pathways for pain has strengthened the understanding of the processing of cutaneous pain in preverbal children. Future research needs to address the processing of pain especially in regard to the less evident types: deep somatic, visceral, and neuropathic. Beginning research has demonstrated that analgesia and anesthesia are effec-tive in ablating adverse stress responses during and after surgery. Continuation of this research focus needs to address the short term and long term physio-logical consequences of untreated pain. Research on the physiological aspects of pain is critical for dev-eloping methods for measuring and treating pain opti-mally.

### *Response to Pain*

Studies on preverbal children focus almost exclusively on the immediate and established pain responses inherent in cutaneous pain. These studies have provided beginning information on how they respond behaviorally and physiologically. This re-search has emphasized *behavioral responses* such as crying, facial expression, and body movement, and *physiological responses* such as heart rate and trans-cutaneous oxygen. While these responses are sensi-tive to painful invasive events, none is specific for pain. Furthermore, most of the research has focused on understanding pain expression in well Caucasian infants undergoing well child procedures such as heel lance, circumcision, and injections at birth through six months of age. While these studies have provided information on how well children respond to imme-diate pain, little is known about how children re-spond to established and long term pain. The few studies that include high risk or ill infants have suggested that responses to pain may be different from those in well children. Thus, studies must include children who are not well.

### *Measurement of Pain*

Procedures for measuring pain are in the exploratory stage of development. For example, measures of cry vary from identifying it to examining finite acoustic parameters. The most accurate and clinically appropriate approach to measuring cry as an indicator of pain has yet to be determined. Similarly, a variety of physiological indicators have been examined in association with immediate pain but their appropriateness as measures of pain has yet to be determined. A few behavioral methods have been developed to measure pain in preverbal children but the methods lack adequate information on psycho-metric properties (Table 3.3). More emphasis is needed on the developmental appropriateness of these tools and their fit with the type of pain being measured.

### *Pharmacokinetics and Pharmacodynamics of Drugs for Children*

Some studies have focused on the pharmacokinetics and pharmacodynamics of drugs used for young infants. While the research in this area is informative for practice, more studies are needed. Expansion of this research is important for adequate management of pain for children.

### *Management of Pain*

Few studies have focused on the pharmacologic and nonpharmacologic management of pain. Pharmacologic research has emphasized pharmaco-kinetics and pharmacodynamics of opioid drugs, dose response, safety of the drug, and methods for drug administration especially for regional and local blocks. Pharmacologic research also has emphasized high technology. Nursing care needed in relation to the use of high technological strategies has yet to be addressed. Comparison of high technological and conventional strategies is lacking in regard to efficacy and cost. Conventional strategies such as the use of NSAIDS and opioids with round-the-clock administra-tion need further examination for safety, efficacy, and appropriate use. Often drug studies include a broad age span of children and adolescents; hence, it is un-clear how applicable the findings are to infants and toddlers. Pharmacologic research must emphasize developmental status with particular attention to premature and term infants under six months.

Studies on nonpharmacologic strategies such as swaddling, nonnutritive sucking, and auditory stimulation/distraction are few in number and pri-marily focus on immediate pain. Other strategies including comforting, distraction, relaxation, child participation, counterirrtitants such as cold, and stimulants such as heat need to be tested for their efficacy. The efficacy of pharmacologic and non-pharmacologic strategies used simultaneously needs to be determined.

Effectiveness of strategies may differ according to characteristics of children such as developmental age, illness status, and type of pain. Thus, research on management of pain should ad-dress child characteristics in establishing the efficacy of singular or multiple strategies.

### *Role of Parents*

Parental participation in caring for the child in pain needs further examination. An unexplored area is pain care of preverbal children by parents and other family members after hospital discharge. With children experiencing day surgery and short hospital stays, parent preparation on managing pain at home needs attention.

### *Integration of Pain Care into Health Care Delivery Systems*

As researchers continue to address the research needs for preverbal children and pain, they should simultaneously focus on how research findings can be integrated into practice. When developing tools to measure pain, researchers must consider the practicality, cost, and feasibility of the tools for clinical practice in addition to psychometric factors. They must address similar factors with pain manage-ment strategies and also determine the provider skill required to implement strategies if they are to be used in a variety of settings. For example, rural hospitals may not have in their employ providers with the expertise to use some of the hightechnological procedures.

### *Research Design Issues*

The designs of the studies comprising the state of the science tend to be descriptive and they often focus on well Caucasian infants under six months undergoing procedures in hospital newborn centers and clinics. Study designs need to be multivariate to appropriately address the multi-dimensionality of pain in preverbal children. The samples need to include preverbal children of differ-ent ethnicities in varying states of health and with different types of pain. A study should incorporate developmental age either as a factor in the design or in the analysis. Settings for studies should be ex-panded to include hospitals, clinics, homes, and day care centers. Inclusion of these suggestions into designs will address many gaps in current knowledge.

## Recommendations

Based on the assessment of research needs and opportunities, the Panel has made the following recommendations for research related to preverbal children and pain. These recommendations apply to cutaneous, visceral, deep somatic, and neuropathic pain and to preverbal children in different settings.

- Expand the basic understanding of the neural pathways for pain in preverbal children.

- Explore the consequences of invasive procedures on the development of neural pathways.

- Differentiate pain responses from irritability and agitation.

· Develop developmentally appropriate tools to measure different types of pain.

· Focus studies on older infants and toddlers in addition to preterm and term neonates and infants under six months.

· Specify pain issues for children with special needs, such as those with multiple handi-caps, disorders of sensory mechanisms, cog-nitive impairments, a history of abuse, mul-tiple invasive procedures such as high risk premature infants, or children or substance abusers.

· Examine the socioeconomic and cultural issues that affect pain expression and management especially for children of different ethnicities.

· Test the effectiveness of pharmacological and nonpharmacological strategies simul-taneously and singly for relieving pain.

· Examine the roles and effectiveness of parents and other family members in caring for children with pain.

· Examine the integration of pain assessment and management procedures into clinical practice.

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